REMARKS

The above amendments to the above-captioned application along with the following remarks are being submitted as a full and complete response to the Official Action dated July 18, 2003. In view of the following remarks, the Examiner is respectfully requested to give due reconsideration to this application, to indicate the allowability of the claims, and to pass this case to issue.

Status of the Claims

Claims 1-4 and 30-37 are under consideration in this application.

Prior Art Rejections

Claims 1-4 and 30-37 were rejected under 35 U.S.C. § 103(a) as being unpatentable U.S. Patent No. 6,251,588 to Shannon et al. (hereinafter "Shannon") and in view of Vijg et al. (WO 98/06872; US 6,007,231, hereinafter "Vijg") and further in view of U.S. Patent No. 6,083,763 to Balch (hereinafter "Balch"). The rejection has been carefully considered, but is most respectfully traversed.

The primer design system according to the present invention, as currently recited in claim 1, comprises means for selecting at least one genomic DNA nucleotide sequence from a database including a plurality of DNA nucleotide sequences; means for predicting a plurality of exons of said selected DNA nucleotide and for storing positions of the predicted exons; means for using each of the predicted exons as a template to design one corresponding primer pair for each of the predicted exons and for designing corresponding primer pairs for the predicted exons simultaneously; and means for automatically collating said plurality of primer pairs with said predicted exons and the DNA nucleotide sequence.

The invention, as currently recited in claim 30, also is directed to a method for designing primers comprising the steps of: selecting at least one DNA nucleotide sequence from a genomic DNA database; predicting a plurality of exons of said selected DNA nucleotide; using each of the predicted exons as a template to design one corresponding primer pair for each of the predicted exons and for designing corresponding primer pairs for the predicted exons simultaneously; and automatically collating said plurality of primer pairs with said predicted exons and the DNA nucleotide sequence.

The invention, as currently recited in claim 34, is further directed a primer design system comprising: means for selecting at least one genomic DNA nucleotide sequence from a database including a plurality of DNA nucleotide sequences; means for predicting a plurality of exons of said selected DNA nucleotide and for storing positions of the predicted exons; means for using each of the predicted exons as a template to design one corresponding primer pair for each of the predicted exons and for designing corresponding primer pairs for the predicted exons simultaneously; and means for evaluating specificity of each designed primer or each designed primer pair.

One main characteristic feature of the present invention is to predict a plurality of exons of selected DNA nucleotide sequences and to design plurality of primer pairs simultaneously by using predicted exons from public databases proceeded via bioinformatics (page 5, lines 4-8) as templates. In other words, the invention involves extensive electronic databases on genomes, protein sequences, etc. By simultaneously designing plural primer pairs for each of the exons, and by simultaneously carrying out PCR using the designed primers corresponding to the exons, the invention **simultaneously and directly** determines exons compatible with a predetermined research purpose at the level of exons. For example, in the analysis of differences in gene levels occurring between normal individuals and patients afflicted with a specific disease, genomic DNAs extracted from the cells of various individuals (healthy or with the disease) are used as templates to carry out PCR using a plurality of primers designed from mutually different exons so as "*to [simultaneously] determine exons related to the disease based on types of their corresponding primers having differences in nucleotide sequences and the length or presence/absence of amplified fragments [between health individuals and patients]* " (page 4, line 21 to page 5, last line). The present invention directly determines exons which are compatible with the research purpose *after* carrying out PCR using primers corresponding to mutually different exons. As such, it becomes easy to analyze DNA fragments amplified by PCR and improve the analysis efficiency. The step of simultaneously designing plural primer pairs for each of the exons makes possible such a direct approach at the exon level of the invention.

On the other hand, the conventional methods (Fig. 7) first identify genes or proteins of interest (with desired functions related to a research purpose) for extracting exons therefrom which ***may be (i.e., relatively remotely)*** compatible with the research purpose, and then design primers corresponding to the exons and carrying out PCR using primers corresponding to each exon (page 3, first paragraph to page 4, first paragraph) to determine **one by one** at the level of

exons whether each exon is compatible with the research purpose via "*trial and error*" (page 4, line 5). "E*xons which are [generally] considered compatible with the purpose of research [based upon the association* ***at the level of genes or proteins****] are selected ...to design corresponding primers... then used in PCR for analyzing the exons* (page 3, first paragraph)" to determines exons compatible with a predetermined research purpose at the level of exons. In other words, the prior art applies a two-stage approach (gene/protein level then exon level), i.e., an indirect approach, rather than a direct approach at the exon level as in the invention.

Applicants respectfully contend that neither Shannon, nor Vijg, nor Balch teaches or suggests "using each of the predicted exons as a template to ***design*** one corresponding primer pair for each of the predicted exons and for designing corresponding primer pairs for the predicted exons **simultaneously**".

Balch is relied upon by the Examiner to make obvious the simultaneously primer-designing for a plurality of predicted exons according of the invention. However, Balch only ***generally*** applies parallel processing of a large number of samples in chemical reactions. "*Large clinical labs process thousands of samples a day, and a microplate configured with a four by four (4 x 4) matrix of biosites in each of the 96 wells would be able to perform a total of 1536 nearly simultaneous tests is from 96 different patient samples utilizing the proximal CCD imager as illustrated in FIG 1.*" (col. 4, lines 40-47; Fig. 1).

Although the invention applies the general concept of parallel processing, the invention applies the parallel processing to design primers for a plurality of predicted exons simultaneously to achieve unexpected results or properties. As mentioned, the step of simultaneously designing plural primer pairs for each of a plurality of predicted exons makes possible a direct approach for determining exons compatible with a predetermined research purpose at the level of exons. The presence of the unexpected property is evidence of nonobviousness. MPEP§716.02(a).

> "*Presence of a property not possessed by the prior art is evidence of nonobviousness. In re Papesch, 315 F.2d 381, 137 USPQ 43 (CCPA 1963) (rejection of claims to compound structurally similar to the prior art compound was reversed because claimed compound unexpectedly possessed anti-inflammatory properties not possessed by the prior art compound); Ex parte Thumm, 132 USPQ 66 (Bd. App. 1961) (Appellant showed that the claimed range of ethylene diamine was effective for the purpose of producing " 'regenerated cellulose consisting substantially entirely of skin' " whereas the prior art warned "this compound has 'practically no effect.' ").*

The unexpected properties were unknown and non-inherent functions in view of the combination of Shannon, Vijg, and Balch ("SVB") as relied upon by the Examiner, since the SVB combination does not inherently achieve the same results. In other words, these advantages would not flow naturally from following the teachings of SVB, since, as admitted by the Examiner (page 4, last paragraph of the outstanding office action), none of Shannon, Vijg, and Balch teaches or suggests "simultaneously designing a primer pair for each of a plurality of predicted exons."

Shannon merely teaches a method for predicting candidates of oligonucleotide sequences that are hybridizable with the target nucleotide sequences. Shannon's comprises an input means for introducing a target nucleotide sequence into computer system by manual input or by using a database and the like, means for determining unique oligonucleotide sequences that are hybridizable with the target nucleotide sequence, memory means for storing the oligonucleotide sequences, means for controlling the computer system to carry out a determination and evaluation for each of the oligonucleotide sequences a value for at least one parameter that is independently predictive of the ability of each of the oligonucleotide sequences to hybridize to the target nucleotide sequence such as Excel or Access, means for automated examination of the stored parameter values, means for carrying out an identification of oligonucleotide sequences in the subset, memory means for storing the oligonucleotide sequences in the subset, and means for outputting data relating to the oligonucleotide sequences which may be machine readable or human readable by using a printer, electronic mail, or oligonucleotide synthesizer (col. 39, lines 1-46). Shannon focuses on determining oligonucleotides that easily hybridize with the target nucleotide sequence. Shannon only teaches one to determine the hybridization ability of the determined sequence by evaluating a parameter such as length of the nucleotide sequence, melting temperature, GC content and the like, but not to design a plurality of primer pairs simultaneously for a plurality of exons so as to determine exons compatible with the purpose of research.

Vijg only *amplifies* exons simultaneously in one two-step PCR process (page 5, line 21 to page 6, line 1), but *designs* the primers based upon one target sequence, such as an exon, at a time (i.e., **one by one**), which is apparent from the statement of step 2 in FIG. 6A which says that "FIND NUMBER OF EXONS, START WITH EXON 1".

Accordingly, even in view of Shannon's teaching of determining oligonucleotides that easily hybridize with the target nucleotide sequence, Vijg's teaching of designing primers for

each exon one by one, and Balch's teaching of parallel processing in chemical reactions, one skilled in the art would not be motivated to design a plurality of primer pairs simultaneously for plural exons thereby determining exons compatible with the purpose of research by carrying out PCR using the designed primers corresponding to the exons.

Applicants further contend that even if, arguendo, one of skill in the art could automate the conventional methods by parallel processing, primer design for a plurality of exons to meet the terms of the claims, this is not by itself sufficient to support a finding of obviousness. The prior art must provide a motivation or reason for one skilled in the art to provide the above-mentioned unexpected property, without the benefit of appellant's specification, to make the necessary changes in the reference. *Ex parte Chicago Rawhide Mfg. Co.*, 223 USPQ 351, 353 (Bd. Pat. App. & Inter. 1984). MPEP§2144.04 VI C.

As such, the present invention as now claimed in independent claims 1, 30 and 34 is distinguishable and thereby allowable over the rejections raised in the Office Action. The withdrawal of the outstanding prior art rejections is in order, and is respectfully solicited.

In view of all the above, clear and distinct differences as discussed exist between the present invention as now claimed and the prior art reference upon which the rejections in the Office Action rely, Applicant respectfully contends that the prior art references cannot anticipate the present invention or render the present invention obvious. Rather, the present invention as a whole is distinguishable, and thereby allowable over the prior art.

Favorable reconsideration of this application is respectfully solicited. Should there be any outstanding issues requiring discussion that would further the prosecution and allowance of

the above-captioned application, the Examiner is invited to contact the Applicants' undersigned representative at the address and phone number indicated below.

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October 14, 2003

SPF/JCM/JT